UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/801,988	03/15/2004	Elias Georges	AUR-016US and 112418.151	2507

23483 7590 02/14/2007

WILMER CUTLER PICKERING HALE AND DORR LLP
60 STATE STREET
BOSTON, MA 02109

EXAMINER	
JOYCE, CATHERINE	
ART UNIT	**PAPER NUMBER**
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	02/14/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 02/14/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

teresa.carvalho@wilmerhale.com
tina.dougal@wilmerhale.com
michael.mathewson@wilmerhale.com

TH

Office Action Summary	Application No.	Applicant(s)	
	10/801,988	GEORGES ET AL.	
	Examiner	Art Unit	
	Catherine M. Joyce	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-77* is/are pending in the application.

4a) Of the above claim(s) *8-77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. The Amendment filed November 15, 2006 in response to the Office Action of August 10, 2006 is acknowledged and has been entered. Claims 1-77 are pending, claims 8-77 are withdrawn from consideration, and claims 1-7 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following rejections are being maintained:

Claim Rejections - 35 USC 112

4. Claims 1-7 remain rejected under 35 USC 112, second paragraph, for the reasons set forth previously in the Paper mailed August 10, 2005, Section 6, page 3.

Applicant argues that the use of the term "greater than" does not render the claims indefinite because the term indefinite has a common usage, which means "comparatively larger in dimension; more considerable in degree, intensity, quantity; or larger in number", as evidenced by Webster's Dictionary, 3rd Ed. (Random House, Ballantine Books, New York, 1998). Applicant further argues that, in the context of the claims, one of skill in the art would recognize that the level of triosephosphate isomerase expression on a test neoplastic cell must be detectably "greater than" the level of triosephosphate isomerase identified on a control, nonresistant, neoplastic cell. Applicant further argues that the specification teaches at page 20, lines 19-26, that a control, nonresistant neoplastic cell is a control cancer cell that has detectably less cell surface expression of triosephosphate isomerase than multidrug resistant cancer cells, an that a control, nonresistant neoplastic cell merely provides a detectable level of cell surface-expressed triosephosphate for comparison against the level of cell-surfaced expressed triosephosphate isomerase detected on the test neoplastic cell. Applicant further argues that the exact degree of increased cell surface triosephosphate isomerase expression on the test cell as compared to the control nonresistant, neoplastic cell is not important as any amount of triosephosphate isomerase that can be detected greater than the amount on the cell surface of the control cell is indicative of

multi-drug resistance. Applicant further argues that claim 1 has been amended to recite that level of cell surface-expressed triosephosphate isomerase in the test neoplastic cell is detectably greater than the level of cell surface-expressed triosephosphate isomerase the control cell.

Applicant's arguments have been considered but have not been found to be persuasive. Applicant argues that one of skill in the art would know the meaning of the term "greater than". However, although one of skill in the art would be able to understand the words "greater than", one of skill in the art would not know the metes and bounds of the claims because one of skill in the art would not know what degree of "greater than" would allow one of skill in the art to determine that a test neoplastic cell is multidrug resistant or has multidrug resistance potential. Applicant further argues that any amount of triosephosphate isomerase that can be detected on the cell surface of a test neoplastic cell greater than the amount of triosephosphate isomerase detected on the cell surface of the control-nonresistant neoplastic cell is indicative of multi-drug resistance and that any difference in triosephosphate isomerase expression between two samples is sufficient, even presumably including a de minimis difference in expression. However, one of skill in the art would recognize that any two samples are not likely to give exactly the same result when measured for triosephosphate isomerase expression levels, and thus any two samples are likely to have at least a de minimis difference in a level of expression whether or not the samples differ with regard to multidrug resistance or multidrug resistance potential. Thus, one of skill in the art would not be apprised of what level of difference in triosephosphate isomerase expression is likely to indicate a difference in multidrug resistance or multidrug resistance potential, and thus one of skill in the art would not be reasonably apprised of the scope of the invention. Amending the claims to recite that the amount is "detectably greater than" the amount on a control cell does not cure the defect that one of skill in the art would not know what level of difference in triosephosphate isomerase expression is likely to indicate a difference in multidrug resistance or multidrug resistance potential.

Thus, Applicant's arguments that one of skill in the art would know how to use the claimed product inventions are not found to be persuasive.

5. Claims 1-7 remain rejected under 35 USC 112, second paragraph, for the reasons set forth previously in the Paper mailed August 10, 2005, Section 8, pages 3-9.

Applicant argues that a correlation exists between established cancer cell lines and primary tumors and that those in the art have long relied upon cell lines to provide reliable and predictable data on cancer and multidrug resistance because cell lines mimic in vivo cancer phenotypes (Applicant cites Gao et al., 2000, Mol. Pharmacol. 58(5)1001-10) as supporting this argument). Applicant further argues that data from cell lines have led to the discovery of important markers of cancer proliferation and drug resistance (Applicant cites Falzon et al., 2000, Endocrinol. 141(5):1882-92 as supporting this argument). Applicant further argues that the cell lines used in the Examples are well known models for cancer and drug resistance, and are recognized in cancer research as being predictive of the in vivo behavior of cancer cells (Applicant cites Gao (2000) and Falzon (2000) as supporting this argument). Applicant further argues that in light of the art recognized correlation (i.e. between established cancer cell lines and primary tumors) and the teaching in the specification, merely routine experimentation would be required to practice the claimed invention.

Applicant's arguments have been considered but have not been found to be persuasive. Applicant's arguments that cell lines have been used to study cancer, to study the development of chemoresistance in cancer, and to identify markers of cancer proliferation and drug resistance are not sufficient to establish that a correlation exists between cancer cells in vivo and in vitro with regard to triosephosphate isomerase expression. While cancer cell lines have proven useful in the study of cancer and chemoresistance in cancer, any such findings in these studies are useful only to the extent that they are ultimately found to be characteristic of in vivo cancers. Given the teachings of the prior art, as set forth in the prior Office Action, on the unpredictability of a correlation between cell lines and cell lines in vivo and the prior art teaching cited by the instantly considered Office Action response, although some correlations have been

established between cancer cell lines and in vivo cancers for expression of certain proteins, genes, and characteristics, the prior art as a whole teaches the lack of a predictable correlation between cancer cell lines and in vivo cancer cells, and thus a predictable correlation between triosephosphate isomerase expression in cancer cell lines and in *in vivo* cancers has not been established. Thus, the rejection is maintained for the reasons set forth in the previous Office Actions.

It is noted that the cited Falzon et al. (2000) and Gao et al. (2000) were not submitted as part of the response and thus could not be specifically considered.

6. Claims 1-7 remain rejected under 35 USC 112, second paragraph, for the reasons set forth previously in the Paper mailed August 10, 2005, Section 9, pages 8-9.

Applicant argues that the cited Tockman reference does not establish that a marker must be tested against population studies prior to being recognized or established as a diagnostic marker and that those skilled in the cancer research art have identified markers without such testing (Applicant cites Falzon et al. (2000), Gao et al. (2000), and Peterson et al., 1991, Biochem. Biophys. Res. Commun. 179(1):661-7 to support this argument). Applicant further argues that those of skill in the art would understand that the Tockman reference teaches the steps required to obtain regulatory approval, such as FDA approval, for the use of such markers. Applicant further argues that those of skill in the art would recognize that the invention works for its intended purpose because the cell lines are well known models for cancer that have been used extensively prior to the filing of the above-referenced application (Applicant cites Falzon (2000), Gao (2000), and Peterson (1991)). Applicant further argues that cell lines are considered reliable models that produce data that is predictive of cancer and multidrug resistance in vivo, and that accordingly, the specification enables the claimed invention without the need for further validation because one of skill in the art would expect that the claimed invention works for its intended purpose.

Applicant's arguments have been considered but have not been found to be persuasive. Applicant's arguments that the cited Tockman reference does not establish

that a marker must be tested against population studies prior to being recognized or established as diagnostic marker is not supported in view of the explicit statement in Tockman that "[p]rior to the successful application of newly described markers, further cross-disciplinary research must ....: (d) confirm marker predictive value in prospective population trials" and in view of the fact that the instantly claimed method encompasses the use of the measurement of triosephosphate isomerase levels for use in predicting the eventual development of chemoresistance i.e. "the multidrug resistance potential" of a test neoplastic cell. Thus, while establishing markers as diagnostic markers may not require prospective population trials but may only require the validation of the marker as a diagnostic marker on clinical samples, Tockman clearly teaches that establishing a marker as having predictive value requires prospective population trials. The argument that Tockman teaches how to establish a marker as a clinically relevant marker for the purposes of FDA approval is also not found to be persuasive. While it is certainly likely that predictive cancer biomarkers approved by the FDA will certainly have been validated prior to FDA approval, the general teaching of Tockman is that predictive cancer biomarkers, in order to be useful as such, much be validated. Further, there is no mention of FDA requirements in the Tockman article. Further, given the knowledge in the art that applications of markers to clinical cancer assessment may or may not be FDA approved, one of skill in the art would interpret the teaching of the Tockman article to apply generally to the development of predictive cancer markers, whether or not FDA approval of the marker application is sought. Thus, the rejection is maintained for the reasons set forth in the previous Office Actions.

It is noted that the cited Falzon et al. (2000), Gao et al. (2000), and Peterson (1991) were not submitted as part of the response and thus could not be specifically considered.

New Grounds of Rejection

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The limitation of "detectably greater than" has no clear support in the specification and the claims as originally filed. In response to Office Action, the specification was cited at page 26, lines 25-30, and page 30, lines 5-22, as providing support for the amendment. The suggested support is not found persuasive because there is nothing in the specification to suggest that the enhanced level of triosephosphate isomerate in multidrug resistance cells is "detectably greater than" the amount found in control cells.

9. No claims are allowed.

10. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine M. Joyce whose telephone number is 571-272-3321. The examiner can normally be reached on Monday thru Friday, 10:15 - 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley, can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8700.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Catherine M. Joyce
Examiner
Art Unit 1642